Appropriate Antibiotic Therapy for Urinary Tract Infections

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It was stated years ago that physicians pour medicines about which they know little, for diseases about which they know less, into human beings about whom they know nothing.[1] Although as a prophet this wag may have overstated the case as it concerns the therapy of urinary tract infections (UTI), the character of contemporary infectious diseases is, in part, due to the use and abuse of anti-infective agents.[2,3] One has only to look at the rising incidence of gram-negative bacteremia and the emergence of multiple antibiotic-resistant organisms over the past several decades to appreciate the impact physicians have made with these agents.[4,5] Despite the drawbacks, the benefits resulting from the use of antibiotics far outweigh the deleterious effects, a fact perhaps realized most vividly by physicians whose careers reach back to the pre-chemotherapeutic era. The enthusiasm for antibiotics makes them one of the most prescribed groups of drugs in the United States, accounting for 15% to 20% of all new and refill prescriptions.[6] Undoubtedly many of the prescriptions are used to treat persons with UTIs, in light of the fact that UTIs are said to rank second only to upper respiratory infections as the most common infections in the western hemisphere.[7]

Principles of Therapy

Without belaboring the point, how does the physician steer his way through the many antibiotics which are promoted so vigorously by pharmaceutical companies, perhaps in response to the competitive pressures and potential profits of what has become a multi-billion dollar industry? Certain characteristics are desirable in any antibiotic, and it behooves the physician to consider these characteristics when evaluating the potential usefulness of the agent.[8]

1. *Activity.* An agent with bactericidal activity against a wide spectrum of microorganisms, and one that doesn't disturb normal flora or lead to the emergence of resistant organisms should be sought.

2. *Toxicity.* Adverse reactions should be infrequent, and teratogenicity absent.

3. *Pharmacology.* Pharmacologic properties should be such that adequate concentrations of the drug are achieved and maintained near the organism for prolonged periods.

4. *Physicochemical properties.* The drug should be stable (dry or in solution) tolerant of pH changes, and readily absorbable from the gastrointestinal (GI) tract.

5. *Interactions.* The drug should not interact with other therapeutic agents.

6. *Cost.* The agent should be inexpensive and hence available to all who need it.

Of course, no such "magic bullet" exists, and because it doesn't, one should be guided, when treating UTIs, by certain fundamental principles.[9]

1. The presence of a bacterial infection should be established. Symptoms alone are not sufficient evidence for the diagnosis of UTI, as up to 50% of women with dysuria and frequency have sterile urine.[10] The finding of one or more bacteria per oil field in a Gram stain of uncentrifuged urine correlates

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well (over 90%) with the presence of 100,000 organisms or more per ml of urine. Numbers of this magnitude usually indicate true infection (significant bacteriuria) and not procurement contamination with gram-negative enteric bacilli. In an asymptomatic person, three consecutive daily urine cultures obtained by the clean-voided method and each containing 100,000 organisms per ml of the same bacterium indicate that the patient has at least a 95% chance of having a UTI.[11] In a symptomatic person, bacteria seen on microscopic examination and one urine culture containing 100,000 organisms or more per ml carries the same 95% probability of true infection.

2. The elimination of bacteriuria requires the use of antibiotics which are active against the common urinary pathogens and which achieve inhibitory concentrations in the *urine,* not the serum. Disappearance of bacteriuria correlates well with the sensitivity of the organism to achievable urinary levels.[12,13] This serves to underline the obvious discrepancies sometimes seen between antibiotic sensitivities in vitro and the eradication of bacteriuria.

3. Underlying urinary tract abnormalities, particularly obstructive or neurogenic lesions, should be corrected if possible; obstruction from whatever cause not only has a compromising effect on renal function but it also practically eliminates the likelihood of successful antibiotic therapy.

4. The hallmark for the eradication of infection is the absence of bacteriuria following the cessation of therapy. Symptomatic improvement is a poor indicator of successful therapy because symptoms may improve with only the slightest suppression of bacteriuria. In addition, while bacteriuria may disappear during therapy, recurrence of the original organism (see below) is common and can be detected only by obtaining cultures after the completion of therapy.

5. Prolonged follow-up is required to insure permanent cure of the UTI. Recurrence of an initially symptomatic and apparently successfully treated infection may be asymptomatic, and constant vigilance by the physician can pay dividends in reduced morbidity from UTIs. This is done usually by obtaining periodic urine cultures (Figure). A culture obtained between 48 to 72 hours after the initiation of therapy should be sterile. If it is not, then the therapy should be recognized as a failure and the patient should be treated with an appropriate antibiotic chosen on the basis of sensitivity tests. If the culture is negative, additional cultures should be obtained one to two weeks following completion of therapy, monthly for three months, then at three-month intervals for one to 1½ years. The patient should be considered cured if there is no recurrence during the period of observation.

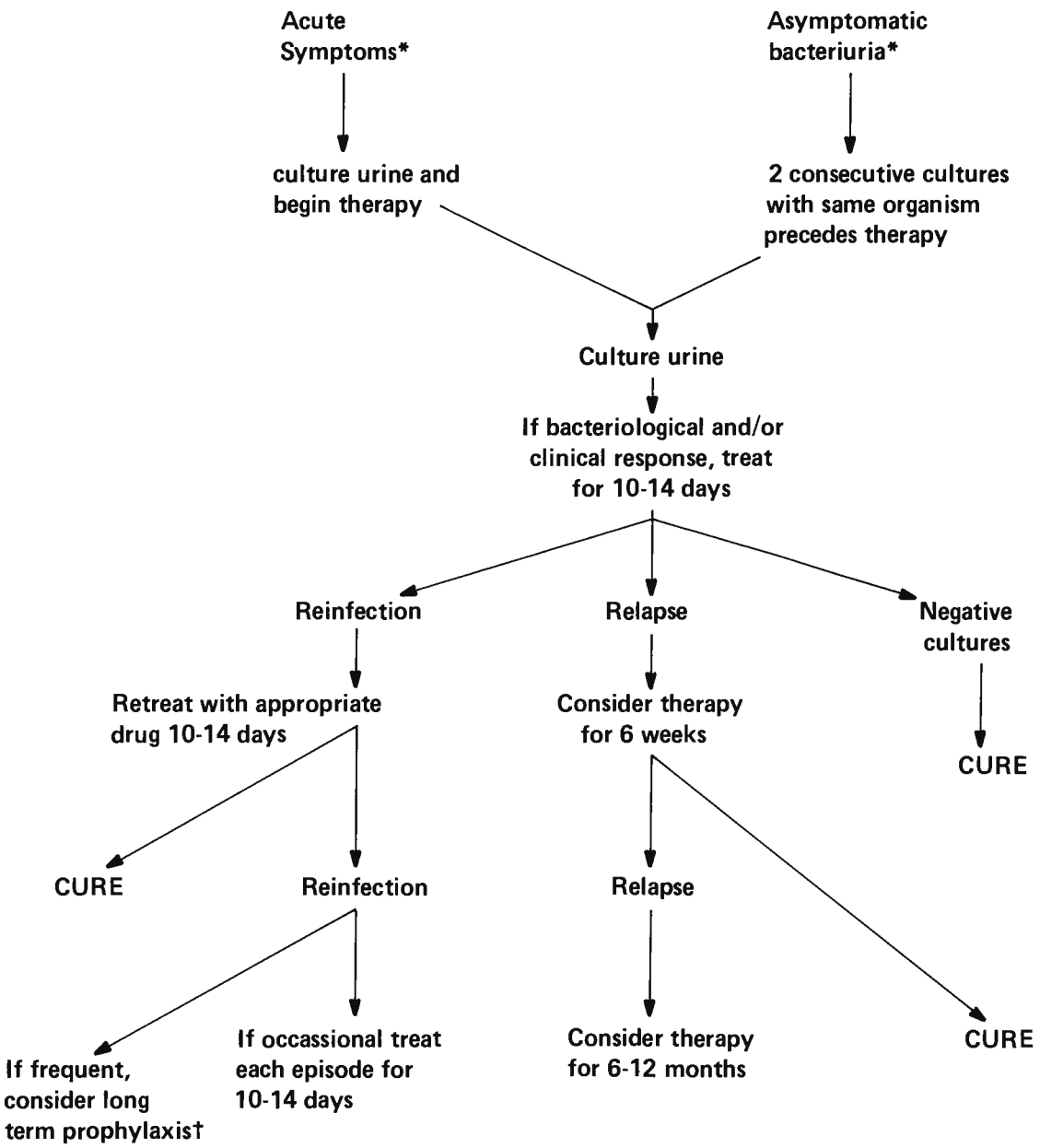
Therapeutic Agents

The goal of therapy for UTIs is the elimination of bacteriuria and the most effective way of achieving this is with antibiotic therapy. The antimicrobial agents frequently used to treat UTIs are listed in the Table. Most share the common characteristics of being active against the majority of common urinary tract pathogens and being excreted at high concentrations into the urine.

Sulfonamides. The sulfonamides were the first group of agents shown to be consistently useful for treating UTIs. Many effective sulfonamides are available, but the short-acting, oral nonabsorbable drugs, such as sulfisoxazole and sulfamethoxazole, are generally recommended. These agents achieve high urinary concentrations and are soluble at an acid pH. Toxicity is relatively infrequent. They are especially effective against *Escherichia coli* and *Proteus mirabilis* but generally are useful only for the first few episodes of infection because of the emergence of resistant bacteria. Although sulfonamides offer no real advantage over other agents, they are inexpensive (see Table) and hence available to most patients. Sulfonamides should not be used in persons with glucose-6-phosphate dehydrogenase deficiency, in pregnant women near term, and in newborn infants because of the danger of producing kernicterus in the neonate.

Penicillins. Among the penicillins, ampicillin remains the drug of choice for UTIs. It is effective against many gram-positive and gram-negative organisms and reaches adequate levels in the renal medulla. Ampicillin is the preferred agent for pregnant women and newborns, and is especially useful in treating UTIs due to susceptible organisms in patients with renal insufficiency. There is no evidence to indicate that ampicillin is superior to sulfonamides in the management of uncomplicated UTIs (see below), just as there is no evidence to indicate that newer penicillin derivatives, such as amoxicillin, are superior to ampicillin. Diarrhea is frequent and rashes occur in 5% to 10% of patients.[1]

Tetracyclines. The tetracyclines have been relegated to a less prominent role in the treatment of UTIs. The best urinary levels are achieved with tetracycline and oxytetracycline.[11] Newer derivatives,



* Radiographic evaluation should be obtained on all children, all men, young women, and probably in all patients with bacteremia

† Not in asymptomatic elderly without obstruction

Figure—Diagrammatic approach to the management of urinary tract infections.

TABLE
Antibiotics Useful in the Therapy of Urinary Tract Infections in Adults

Antibiotic	Tradename(s)	Dosage[a]	Cost in dollars (dose)[b]
Oral:			
Sulfisoxazole	Gantrisin	0.5-1.0 gm q 4-6 h	.04 (0.5 gm)
Sulfamethoxazole	Gantanol	1.0 gm q 8-12 h	.08 (0.5 gm)
Penicillin G	Many	0.4-0.8 × $10^6\mu$ q 6 h	.01 (0.2 × $10^6\mu$)
Ampicillin	Many	0.5-1.0 gm q 6 h	.09 (0.5 gm)
Amoxicillin	Larotid, Amoxil	0.25-0.5 gm q 8 h	.30 (0.5 gm)
Tetracycline	Many	0.25-0.5 gm q 6 h	.03 (0.5 gm)
Cephradine	Velosef, Anspor	0.5 gm q 6 h	.56 (0.5 gm)
Cephalexin	Keflex	0.5 gm q 6 h	.52 (0.5 gm)
Nitrofurantoin	Furadantin	0.05-0.1 gm q 6 h	.01 (0.05 gm)
	Macrodantin	0.05-0.1 gm q 6 h	.15 (0.05 gm)
Nalidixic acid	NegGram	0.5-1.0 gm q 6 h	.12 (0.5 gm)
Trimethoprim-Sulfamethoxazole	Bactrim, Septra	2 tablets q 12 h	.21 (per tablet)
Parenteral:			
Ampicillin	Many	0.5-2 gm q 4-6 h	1.11 (1 gm)
Carbenicillin	Geopen, Pyopen	1-5 gm q 4-6 h	2.20 (1 gm)
Cephalothin	Keflin	0.5-2 gm q 4-6 h	2.75 (1 gm)
Cefazolin	Ancef, Kefzol	0.5-1.5 gm q 6-8 h	5.05 (1 gm)
Gentamicin	Garamycin	1-1.7 mg/kg q 8 h	5.05 (per 80 mg vial)
Amikacin	Amikin	5 mg/kg q 8 h	4.93 (per 100 mg)

[a] Usual average or range of dosages in patients with normal renal function.
[b] Cost to pharmacist based on listings in the American Druggist Blue Book (Hearst Corp. Publishers), October 1977.

such as doxycycline and minocycline, although approved for use in UTIs, have significant extrarenal routes of excretion, so that the low urinary concentration achieved makes them less desirable for therapy.[14] Generic tetracycline is inexpensive (see Table). Resistance to tetracycline emerges rapidly during therapy; however, tetracyclines are probably as effective as the sulfonamides and ampicillin for treating uncomplicated UTIs (see below). Fulminant hepatitis has been induced in those receiving large parenteral doses of tetracycline (greater than 2 gm per day), and irreversible discoloration and maldevelopment of permanent teeth is a danger in children under age 8 who receive these drugs[14]; however, GI signs and symptoms are the most common side effects of therapy.[14]

Cephalosporins. The instances where cephalosporin antibiotics should be used are difficult to define, but they are indicated possibly for treating gram-positive coccal infections (except those caused by enterococci and methicillin-resistant staphylococci) in patients allergic to penicillin. These agents are useful in treating infections due to *Klebsiella pneumoniae* and antibiotic strains of *E coli, P mirabilis,* and other gram-negative bacilli. The use of cephalosporin antibiotics for central nervous system infections is contraindicated.[15] Although most of these drugs achieve good urinary levels, and are therefore effective agents for the therapy of UTIs, most are expensive (see Table) and should not be used when cheaper, equally effective drugs are available. The two most important oral agents, cephalexin and cephradine, are similar and can be used interchangeably.[16] Up to 5% of patients develop allergic reactions such as rash, fever, and, rarely, anaphylaxis[17]; 5% to 15% of penicillin-allergic patients will manifest allergy to the cephalosporins.[18]

Aminoglycosides. The aminoglycoside antibiotics are parenterally administered agents useful against a wide variety of gram-negative organisms. These drugs have the potential for causing significant oto- and nephrotoxicity[19] and should therefore be reserved for therapy of hospitalized patients with moderate to severe UTIs caused by organisms resistant to less toxic agents. Dosage should be adjusted for those with renal insufficiency; such alterations in dosage can be achieved by any of several published programs.[20-22] Gentamicin and amikacin are two commonly used aminoglycoside antibiotics which differ little in the incidence of toxicity.[23] However, amikacin is resistant to many more of the aminoglycoside-inactivating enzymes than gentamicin,[24] therefore its

greatest utility at present is in the therapy of UTIs caused by gentamicin-resistant organisms.

Nitrofurantoin. This drug is available in crystalline and macrocrystalline forms. The latter compound is absorbed from the GI tract and excreted more slowly than the crystalline form and allegedly causes less GI upset. Nitrofurantoin achieves high urine concentrations and is more active at an acid pH. It is effective against gram-positive and gram-negative organisms except *Pseudomonas* sp, some *Enterobacter* sp, *Serratia marcescens,* and indole-positive *Proteus.* The drug may be useful for lower *and* upper UTI.[11] Nitrofurantoin is contraindicated for use in patients with renal failure because little of the drug is found in the urine and because the incidence of irreversible peripheral neuropathy is increased under these circumstances.[11] Small amounts of this orally administered drug is found in the feces, which probably accounts for the relatively low incidence of resistant enteric organisms emerging during and after therapy. Thus, nitrofurantoin would appear to be a useful therapeutic and prophylactic agent for patients with recurrent UTIs[25] (see below).

Nalidixic acid. Nalidixic acid and its cogener, oxolinic acid, are oral antimicrobials which have virtually the same antibacterial spectrum, including most gram-negative urinary tract pathogens except for *Pseudomonas* sp, *Serratia marcescens* and indole-positive *Proteus.* Resistance develops rapidly and recurrence of infection with resistant organisms is not uncommon. Blood and, presumably, tissue levels are low. These agents are moderately expensive (see Table) and should be used as alternative therapy to other oral agents such as the sulfonamides and ampicillin.

Methenamine salts. Methenamine salts have a limited role in the therapy of UTIs. These agents are effective against most gram-negative organisms in vitro, but require an acid medium (pH of 6 or less) for release from methenamine of the bactericidal agent formaldehyde; tissue levels are low to absent. The main uses are for suppression of bacteriuria or prophylaxis between episodes of infection. The efficacy of methenamine salts in patients with chronic indwelling bladder catheters recently has been questioned.[26]

Trimethoprim-sulfamethoxazole (TMP-SMX). TMP-SMX is a fixed combination of drugs which acts additively or synergistically against a wide range of gram-positive (including enterococci) and gram-negative organisms, except *Pseudomonas* and *Alcaligenes* sp. The list of indications for TMP-SMX continues to grow and presently includes infections due to *Shigella* sp, *Salmonella typhi,* ampicillin-resistant *Haemophilus influenzae,* and *Pneumocystis carinii,* and diseases such as acute exacerbations of chronic bronchitis, acute otitis media, and gonococcal urethritis.[27] Its most practical applications are the treatment of and prophylaxis for recurrent UTIs caused by susceptible organisms.[25] Emergence of resistant organisms in the fecal flora has not been a major problem and because trimethoprim penetrates prostatic tissue, TMP-SMX is probably the drug of choice for recurrent or chronic prostatic infection.[28] The adverse effects of TMP-SMX represent the sum of reactions to trimethoprim (folate deficiency syndromes and possible teratogenic effects) and sulfamethoxazole (see above). The drug may be used in mild-to-moderate renal failure.[29]

Urinary Tract Infections

Urinary tract infections represent a broad group of clinical entities with bacteriuria as the common thread. Many classifications are possible, but those which include not only the type of infection but also the site of involvement allow for the most accurate assessment of antibiotic therapy. Although the site of infection in many instances is unknown, enough evidence is available to analyze antibiotic therapy in the following clinical categories of UTI: acute uncomplicated UTI; recurrent UTI; complicated UTI; asymptomatic bacteriuria; and catheter-related UTI.

Acute uncomplicated UTIs usually represent the first or second infection in young sexually active women without underlying urinary tract abnormalities, and are caused by antibiotic enteric bacilli (most commonly *E coli*) which emanate from antibiotic fecal flora. This type of infection responds well to practically all commonly used oral antibiotics, but because they are effective, inexpensive, and well-tolerated, the oral, nonabsorbable sulfonamides remain the therapy of choice. Treatment is usually given for 7 to 14 days. Longer courses of therapy are usually not necessary. Many alternative agents exist (see Table), but none have proven superior to the sulfonamides and most are more expensive. In the absence of an obstructive or neurogenic lesion, the urine should be sterile between 48 to 72 hours (Figure). If bacteriuria persists, therapy should be guided by the results of sensitivity testing.

Some patients with acute symptomatic infection

fail to respond to the initial antibiotic therapy or suffer *recurrence* of the infection. The recurrence may be a *relapse* of the initial infection with the same pathogen, suggesting a parenchymal focus of infection in the kidney or prostate or may be caused by different organisms, so-called *reinfections*. The source for reinfection is almost always the bowel flora. Approximately 80% of recurrences are reinfections and most are limited to the bladder. Antibiotic sensitivity testing assumes added importance in this situation because the pathogen will probably not be sensitive to sulfonamides if used initially. Ampicillin, tetracyclines, cephalosporins, and TMP-SMX are preferred and are given orally for 10 to 14 days. Each course of therapy will result in a 20% to 25% long-term cure rate.[11] Those having a second or third episode of infection should probably be evaluated urologically or radiographically (see Figure). Those with occasional recurrences (three or less per year) can be treated like acute uncomplicated infection. With more frequent recurrences, especially in the absence of urological abnormalities, the precise duration of therapy is not well established. Closely spaced recurrences are likely to be due to relapse and some have suggested treating true relapses for six weeks to one year.[10] Most authorities suggest six weeks of therapy with the realization that the optimal duration of therapy for this group of patients is controversial. An alternative approach consists of intensive initial treatment for 10 to 14 days, followed by daily low-dose nitrofurantoin (100 mg) or TMP-SMX (one half to one tablet). Prophylaxis should be continued for up to six months, then discontinued, and the patient observed.

Acute complicated UTIs are a third category of infections; they are almost always associated with underlying genitourinary tract or neurological disorders. Isolated organisms tend to be multiply drug-resistant. Permanent eradication of the bacteriuria is unlikely, but the goal is to control symptoms. Initial therapy ideally should be based on sensitivity studies, but pending culture results, an aminoglycoside antibiotic, that is, gentamicin, is an obvious choice. Therapy for 10 to 14 days is usually adequate. Emergence of resistant organisms in this setting is a probable event.

Asymptomatic bacteriuria represents a large group of UTIs with an incidence ranging from 1.2% in pre-school girls to over 15% in women over age 60.[11] Certain groups are known to be at risk for acquiring significant asymptomatic bacteriuria and subsequent symptomatic UTI. Included are pregnant women in the first trimester, women with diabetes, preschool- and school-age girls, and those with a previous history of urinary tract instrumentation. About 5% of pregnant women will have asymptomatic bacteriuria at the first prenatal visit and 20% to 40% of these will develop acute pyelonephritis.[9] Assuming that acute renal infection in the mother contributes to prematurity and fetal mortality, treatment should be initiated. The preferred agents are the penicillins, cephalosporins, nitrofurantoin, and short-acting sulfonamides (first trimester only). Treatment will eliminate bacteriuria in 80% of these patients. Some will have recurrence and for these patients, nightly prophylaxis through term with nitrofurantoin is recommended. The necessity to treat other groups of patients with asymptomatic bacteriuria is less certain, especially elderly women in whom bacteriuria tends to be recurrent even in the absence of underlying disease. Available evidence indicates that, in adults, progressive renal damage due to UTI is an uncommon occurrence in the absence of obstruction.[10] Several attempts at eradication seem worthwhile. If bacteriuria recurs, genitourinary evaluation is warranted. If no abnormalities are found, no further therapy is necessary in the elderly.

Catheter-related infections are the most common hospital-acquired infections and the most frequent causes of gram-negative bacteremia.[4,11] Patients acquiring bacteriuria with short-term closed drainage should be treated with an effective antibiotic for 7 to 10 days after the catheter is removed. Long-term drainage represents a different problem. Patients on long-term drainage are continuously infected but usually do well. Antibiotics will not clear bacteriuria permanently while the catheter remains in place. Therapy is reserved for acute episodes of infection.

A scheme for the management of patients with bacteriuria is given in the accompanying Figure. It is meant to serve only as a guide for the practicing physician and should be modified in light of future improvements in the diagnosis, localization, and therapy of UTIs. Optimal therapy awaits a more precise classification of UTIs, the end result of which will be a reduction in morbidity and mortality from UTIs, and a significant decrease in the cost of related health care.

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